Ozlem Goker-Alpan:

Hello, everyone. I'm Ozlem Goker-Alpan. I'm the host of CME Series on Lysosomal Disorders. And for today, we are going to be talking about cardiac structural abnormalities and arrhythmias in lysosomal disorders or generally lysosomal disorders and the heart. So I would like to welcome everyone to this last presentation of this series for this year. And after this, we are going to be looking for the next series of this program, which is actually very well sought after.

I just want to have a brief introduction for this. The reason is we'll have Dr. Jeffries, who is going to be presenting in detail on this subject. So I just want to go over the lysosomal disorders with prominent cardiac involvement. And to the right side of the screen, you're seeing this fancy image. This is the T1-T2 mapping for Fabry disease that Dr. Jeffries will be talking in detail.

So cardiac involvement is a common presentation in lysosomal disorders, either the primary culprit or due to secondary involvement, but we have major disorders, sphingolipidoses or GAG metabolism disorders, MPS and mucolipidosis that can present as the primary cardiac disease. In addition, Pompe disease actually presents in the infantile form as the primary cardiac disease and then a disease, which is a muscle disorder X-linked due to lysosomal associated membrane protein deficiency.

So as pathophysiology, if we need to think about the actual culprit, why heart is getting involved in lysosomal disorders, we can start with the sphingolipidoses. Obviously Fabry disease is the poster disease for this group of disorders where there is primary cardiac involvement.

So obviously that we can talk about the substrate accumulation, such as GB3, glucocerebroside. In Gaucher disease, there's a subtype with cardiac involvement. And discuss the lysosomal abnormalities, including lysosomal membrane permealization, release of lysosomal enzymes and triggering mitochondrial energy dysfunction and the apoptosis of the cells. But there is a general impair autophagy. Mitophagy has been implicated in the cardiac involvement.

That actually takes us to the secondary signaling cascades that will give rise to the inflammatory process or the cascade that is common to every single lysosomal disorder, such as the MTOR hyperactivation, TFIIB suppression that worsens this lysosomal biogenesis, TGF beta upregulation. If I need to remind, TGF beta is the master regulator of the fibrosis. Or the NF-kBeta mediated release of IL-6 and the TNF-alpha that sustains the chronic myocardial inflammation and the remodeling. And obviously ceramide and sphingosine-1 phosphate imbalance had been implicated in the [inaudible 00:03:42] apoptotic process and dysregulation cardiomyocytes calcium handling. And this actually ends up with the reduced endothelial nitrous oxide bioavailability that may give rise to microvascular disease and diastolic dysfunction that we see primarily at the early Fabry disease cardiomyopathy.

When we look at the NPS and mucolipidosis, it is a little different than the sphingolipidoses because GAGs actually are the components of the connective tissue. And the GAGs are hydroscopic that lead to tissue expansion that may compress the adjacent structure and disrupts the extracellular metrics and architecture. And direct inhibition of elastin cross-linking by heparin sulfate reduces valve and vessel compliance. And chondroitin sulfate in valve spongiosa expands and weakens the leaflet coaptation zone.

And similarly, there are the inflammatory and secondary mechanisms due to GAG depositions such as GAG activated microphages infiltrating valve leaflets, MMP2 and MMP6 upregulation, and also misrouting of the enzymes such as in ML2 and three that amplifies the extracellular GAG accumulation.

So if we think about the arrhythmias, they obviously can originate from the damaged tissue such as in Fabry disease, but also the substrate could be a culprit for the iron channel on autonomic basis of the disease, such as the GV3 autonomic ganglia impairs this sympothovagal balance causing sinus node dysfunction and chronotherapy incompetence in Fabry disease.

Ceramide and sphingosine-one phosphate imbalance can modulate the cardiac voltage and L-type cardiac calcium channels and prolonging the QTC interval. And similarly, mitochondrial dysfunction can be actually a reason for the arrhythmias that we observe in lysosomal disorders as a reason for photophysiology.

But obviously, even though we discuss some divergent phenotypes, there are shared convergent mechanisms across all lysosomal disorders, including the lysosomal dysfunction activating the MTOR causing hypertrophy and suppressing the TFIIB due to or leading to impaired lysosomal biogenesis. And in both groups, there is NF-kBeta-driven chronic inflammation and both groups, there is progress in myocardial fibrosis and there are both in both groups. There is the ER stress, UPR activation, and substrate excess promoting cardiomyocyte death and apoptosis.

So before I give the word to Dr. Jeffries, then I would like to thank to our supporters of the program, Takeda Enterogenic.

So now I would like to introduce Dr. Jeffries, who obviously needs no introduction. Dr. Jeffries is a world-renowned cardiologist that is on the rare disorders as it relates to the heart that includes the cardiomyopathies, heart failure, and cardiovascular genetics. And also among the last research interests, obviously using AI in the genetic cardiac diseases actually is getting a much recognition for Dr. Jeffries, who is currently a professor at University of Memphis. He's also the immediate past governor of the Tennessee Chapter, American College of Cardiology and President of the American Heart Association with SAR chapter. He also has a research faculty membership at St. Jude's Research Children's Hospital.

Dr. Jeffries, please take on for today's presentation.

John Jefferies:

Thanks. Thanks, everyone, and appreciate the opportunity, and hopefully my screen is coming through easily. So thanks again, and thanks for the kind words as well. Very kind. And Ozlem did a great discussion there about some of the basics behind what drives some of the phenotypic disease we see. I'm going to scope back up and give you some ideas about how we diagnose the disease, some of the phenotypic considerations, and then also maybe some of the management opportunities. And I'll try and stay on time. We have a lot of information, but I definitely want to save time until the end where we have some opportunities just to have a dialogue about any questions that you may have.

So what we'll do today is we'll introduce some of the ideas around the heart and the implications in patients with lysosomal disorders. How does the cardiologist fit into this whole schema? And then some ideas about how do we use this information to manage patients? And so these will be our learning objectives. And once again, we'll talk a little bit about more about arrhythmias. We'll talk some of the cardiomyopathy phenotypes and a little bit about heart failure management.

So we know the cardiovascular implications are significant. We've heard some of the disease processes mentioned earlier, obviously cardiovascular disease leading cause of mortality in Fabry disease, infantile Pompe. And so it really behooves us to be cognitive of the potential CV morbidity and mortality at an early onset and institute appropriate therapies based on their diagnosis. But then really it really comes back to the surveillance and how quickly are we responding to changes that we see on imaging or on electrocardiographic surveillance.

Just a brief word on Pompe. We'll spend most of our time talking about Fabry, and then we'll actually spend a fair amount of time just talking about general principles when it comes to myocardial dysfunction, so heart failure, and then arrhythmia surveillance and management.

So we know infantile Pompe obviously has these dramatic electrocardiographic findings that we see on board questions for pediatric exams or even for pediatric cardiology exams, but we're very well aware

that what's driving that is this significant hypertrophy. And it's typically left ventricular, but if you look at it echocardiographically, oftentimes it's even biventricular. So we have this biventricular hypertrophy, which is reflected in these large QRS complexes that you see on electrocardiography. You see a short PR interval, so that can sometimes be evidence of preexcitation if you saw a delta wave there. Repolarization (repol) abnormalities, which we used to think in large part were benign, but it actually, preexcitation can be one thing, but repol is a very common finding on pediatric electrocardiography. We've started to figure out that repol may have its own important implications for longitudinal outcomes. Obviously, bundle branch and AV block can occur based on what you just heard from OSLAM about the disease substrate and how we're affecting some of the tissue at a local level. And then obviously ventricular arrhythmias and supraventricular arrhythmias can occur.

And this is an important slide. I think this was New England Journal paper from not too long ago. The topic of the paper was really more around the use of enzyme replacement. It shows in two siblings here, very dramatic differences. The top sibling two is untreated, and you see this really profound biventricular hypertrophy, both in a four-chamber view. This is a fetal echo, so it looks a little different than a traditional echo. And then on short axis is where we're cutting the heart like a donut. And then you see the below images of the sibling who was treated with intrauterine ERT, and that's more approaching normal wall thickness, so dramatic differences. But that's really the kind of phenotype that we're talking about in the setting of infantile disease.

Late onset, usually the cardiovascular implications are less severe. There may be left ventricular hypertrophy, but it's not horribly commonplace. And if it is, it's relatively mild. One of the things we do leverage, and you heard this alluded to on cardiac MR, and we'll talk more specifically about cardiac MRI and how to leverage it in clinical practice, is that we know in adults or late onset Pompe patients, we will see evidence of scar. And that's what this LG stands for late gadolinium enhancement. That's evidence that there's some fibrotic mechanism at the myocardial level, and we'll see that in about one in five patients with late-onset Pompe.

We still can see the electrocardiographic disease, so we can see some enhancement of the QR's complexes, and you can occasionally see that short PR interval. But the one thing that I see in and we pay attention to are arterial aneurysms. I've seen thoracic aneurysmal disease, we've seen intracranial aneurysmal disease, and obviously that matters because there are set thresholds for when we would want to talk about intervening surgically on aneurysmal disease, but more importantly, we would typically employ some kind of medical therapy to reduce wall tension on those aneurysms. So that could be in the form of beta blockers, ARBs, other oral therapies that would do to kind of reduce the wall tension, obviously reduce the rate of growth, and hopefully avoid a dissection.

So for Fabry, we'll spend, like I say, a few times on this, and I think this is an important slide. We all know that even in utero, we're depositing substrates. So we know that the potential phenotypic burden is there and it only continues to grow on a daily basis, but ultimately we don't really see evidence of that at an organ level until we have sort of a tipping point, whether we have enough hypertrophy or we have enough involvement in the conduction system where we can detect this. But we all know that this is coming. So one of the things we've advocated for, I think as a cardiovascular specialty in lysosomal disorders is really more about how can we stay ahead of the curve, anticipate what's happening through the appropriate screening, and then intervene as early as possible.

These are some of the findings that, and this is not all-inclusive, but it's pretty close. We know obviously systemic hypertension is relatively common in the setting of Fabry. That can be because of changes at the vascular level when we have infiltrative disease in the vascular wall, but it can also be secondary to upregulation of the RAS system. It can be because of concomitant kidney disease. All the things can be drivers for systemic hypertension. And that hypertension can actually contribute to left ventricular

hypertrophy. Obviously, you can develop LVH in the absence of systemic hypertension, but when someone is hypertensive, it doesn't help. And obviously it's going to accelerate that process potentially.

The heart rhythm and conduction system disease we know are relatively common. We published data a few years ago now that the first findings we typically see electrocardiographically in our pediatric Fabry patients is sinus bradycardia, but we also see other supraventricular arrhythmias can occur, but it just calls out the fact that we do need to be monitoring screening ECGs.

Valvular disease can occur usually just left-sided disease, so mitral and aortic. We don't typically see involvement of the tricuspid or the pulmonic valve. Vasculopathy can occur, and you heard a bit about that in the opening slides. We know ischemic heart disease is a real consideration in Fabry. We can have premature coronary disease, which can lead to ischemia and myocardial infarction. So being cognizant of that and doing appropriate screening such as things like coronary CT angio or stress testing is an important consideration.

We know sudden death is one of the things that we are dealing with more and more as our population ages a bit. Some of the mechanisms of that are still being sought out, but we think primarily those are driven by ventricular dysrhythmias, and we'll talk a little bit about how you could surveil for that and offer protective strategies for your patients. And then aortic dilation we talked about where we can't see thoracic aneurysmal disease.

And the role of a cardiologist here, I think is an important one just because this is such a leading driver of morbidity and mortality, but it has to be in the realm of a multidisciplinary team. We would be looking for cardiologists usually that are familiar with cardiomyopathy, with heart failure and genetics. And it's ideal to have members of both the adult cardiology team and the pediatric cardiology team. There are lots of cardiologists, as you're probably aware, they're familiar with heart failure. Cardiomyopathy, not so much so in genetics even less. Sometimes it's challenging to find these team members, but they do exist, but they really do enhance the delivery of care for your patients. As we know, it's multiple phenotypic manifestations, and these things can't be in silos. If you have a patient with kidney disease that has important implications on the heart, just as heart disease has important implications on the kidney. So this idea of crosstalk, I think, is really, really important.

I think you also want other cardiologists that can feed into that central sort of cardiomyopathy provider that have expertise in imaging because that's so much of what we do, whether that's echo, MR, CT, EP, because of the conduction disease and other things we've talked about. Heart catheterizations may be a part of the ongoing care, and then obviously intensive care as it's needed.

I think many on the call know this, but the sphingolipid deposition impacts a lot of the things that matter to me as a cardiologist. Obviously, the valvular disease, we talked about the dysrhythmia, we've talked a little bit about. The endothelium is one that really is important if you think about how our bodies function and also are alluded to NO deficiencies in a lot of these patients, that without that reactivity at the endothelial level, the ability to vasoconstrict and vasodilate becomes disrupted, and that's so mission critical to what we do for end organ function, not to mention the impacts that it has on cardiac function. So the more we learn about this, this obviously would be more of a potential target over time, but one that really does matter in my world a lot.

And then obviously at the cardiomyocyte level, you've heard a little bit about this. You can get changes not only in the cell itself and the function of the cell, but also obviously in the extracellular matrix. And we actually have mechanisms that we can track that with imaging. Some of the cardiac manifestations we'll talk a little bit more about, but being cognizant that low T1 is one of the earliest physiologic biomarkers that we have, you can also look for things like high sensitivity troponemia, other serologic biomarkers, but these are the things that we sort of pay attention to. They give us a lot of insights into

not only the initial, what we say, cardiac phenotypes or the earliest stages. But then obviously once you institute therapy, how are you following these patients longitudinally to see how they're responding to therapy?

This is another great slide that's been around for a few years now, but what do we see from a timeline perspective and how things are progressing? You do see we leverage a lot of biomarker testing because that's relatively agnostic and can be done in a lot of different places where things like CMR may have limited opportunity. But we see changes, as we said, in high sensitivity troponin. Ultimately, we'll see changes in natriuretic peptides, things like NT-proBNP. And all of these are evidence one of myocardial damage. So the troponin is going up because we are directly damaging cardiomyocytes.

When we see BNP levels go up, that comes back to the diastolic dysfunction that you heard about in the first few slides. And what that biomarker is evidence that there's increased pressure in left ventricle. It can be secreted because of other involvements, such as the right ventricle, but it's primary, the left ventricle, simply because that's where most of the muscle mass is. And when we start seeing that, that's evidence that we probably have some sort of ongoing increased left ventricular and diastolic pressures, which can lead to things like heart failure with preserved ejection fraction, pulmonary hypertension, some of the things we'll talk a little bit about today. And then you do see all of these progressions over to advanced cardiomyopathy.

Today, we're going to talk a little bit about what are the definitions around heart failure? In cardiology, we love to use a lot of cool acronyms and more about what those acronyms are and how they're defined, which will inform some of the therapeutic options that you may pursue. The takeaway on cardiovascular disease, in my mind, I mean, lysosomal disorder is very straightforward. The earlier you can identify involvement, the better opportunity we have to have a successful outcome from the cardiovascular perspective.

And it's very simple. If a patient is admitted with heart failure today with Fabry disease, these numbers unfortunately are true across heart failure populations in general, is that their mortality curve automatically took a big upswing. And what we would quote general patients in a heart failure clinic is your five-year mortality is probably around 45 to 50% because of that one admission. So our goal is to avoid those admissions as much as possible.

Similarly, if you have a stroke and you've damaged cerebrum or if you have a heart attack where you've damaged myocardium, those are irreversible conditions. And so with a progressive disease, if I layer on an acute insult like an MI, it makes the management much more complicated and it really lends itself to a worse outcome. So anything we can do to stay ahead of these is obviously advantageous. What our goal really in cardiovascular care in my mind is about using the right kind of screening and how active are we and doing these things in a very regular, predictable manner.

And in our clinics, we're very thorough, I think, when it comes to phenotypic characterization, whether that's with imaging, whether that's with electrocardiographic surveillance, whether that's with biomarker testing, and remembering that those are longitudinal opportunities where they have to be done over and over and over, simply because we know that these diseases are progressive in nature.

So let's drill in just a little bit more about arrhythmias. And these arrhythmias, as you heard on the initial slides, are relatively all blanketing when it comes to lysosomal disorders. We see arrhythmias in every lysosomal disorder patient that I see as a potential concern, but there's specific areas that we pay more attention to in others. So for example, we talked a bit about Danon disease in one of the slides. That Danon disease has a profound tendency for heart block, for example, and also for malignant ventricular dysrhythmia. So I would think about those patients a little bit differently and be very thoughtful on how I do surveillance. We talked in Fabry that we know sinus bradycardia is a common finding. We know

conduction system disease is a common finding. And it turns out that atrial fibrillation is a relatively common finding in Fabry disease. Probably between 16 and 20% of adults with Fabry will develop atrial fibrillation. And I can make an argument that that number is probably even higher. We just don't detect most of them.

So we know in Fabry, for example, really broad spectrum, pretty much any dysrhythmia you can name in Fabry. So it could be everything from bradyarrhythmias to tachyarrhythmias to conduction disease. And that's important because both profoundly could be life-threatening and the interventions are important and a little bit different for brady versus tachy.

So we know that conduction disease can happen in patients, and this is a patient who obviously is quite bradycardic and is having some escape ventricular beats. And those are folks that you would be thinking about doing the pacemaker in, for example. But there's even more data that you can glean from just simple electrocardiographic monitoring. So in every EKG, you know that at the top you get a QRS duration, and typically we would say 110 or less is going to be normal for most people.

But when you see that QRS starting to widening, that tells you that there's some abnormality in the way that the electrical activity is being conducting through the ventricular myocardium. And you see a broad and very quick difference in Kaplan-Meier curves here once you see that QRS going below above 110. And when you see these sorts of things, that should probably trigger a thought, well, why would the QRS be lengthening? And that's probably because of deposition, scar tissue, ECV expansion, all the things that we'll talk a little bit more about, but it should clue you in that advanced imaging may be something that should be a part of that patient's care. But profoundly different changes in outcomes just on a simple biomarker that's present on every EKG.

How we do surveillance, and these are just examples. There are plenty of brands that you can leverage in this kind of surveillance, but the top left is just the traditional EKG that every patient is hopefully getting when they're coming in to see a cardiologist. The top right would be a traditional Holter monitor, which you can imagine if I have a patient wear that for 48 to 72 hours, they're not particularly happy with me. It's not the most user-friendly technology is what we would say. But it gives us valuable information, at least for that time of surveillance.

The limitation, as you might imagine, is if you come to see me and I do a Holter as a part of your routine surveillance and it comes back clean, it has a normal number of PVCs, and I recognize all of us have PACs and PVCs, then the patient's going to say, "Well, that means I'm good." And I'm like, "Well, and even clinicians need to be reminded of this." That means at least for those three days, you're okay. Unfortunately, that doesn't tell me about the other 362 days in the year. So that's the shortcoming of Holter monitoring.

So what have we done to try and extend that surveillance period, especially for things like atrial fibrillation? So in the bottom left, you see a wearable pad, and different institutions have different pads that you can use where it's on the external side of the chest. Oftentimes you can take them off, put them back on, and actually have a little button that you can trigger if you're having some sort of suspected event, if you felt presyncopal, for example, and it will timestamp that. And you can get many of these that are wearable for maybe a week. And so you can change them out periodically and get more and more data, but still a little bit of a patient burden and it doesn't give us what we would say true continuous annual surveillance.

The bottom right is really where we've changed our diagnostic capabilities and arrhythmia surveillance. So that is a loop recorder. There are different companies across the world that make loop recorders. They're considered a commodity now in cardiovascular medicine. There's nothing special about them to any great degree. They slip under the skin. And based on the device and the company you're working

with, they can give you continuous surveillance, so every heartbeat for between two and five years, which that's really important for us. That obviates a lot of the things you see on the screen, but more importantly it helps me to know that I'm at least paying as close attention as I possibly can to a patient.

Now, those data are typically downloaded. You can download them at will. In addition to the slides you see here, you can actually do continuous continuous telemetry if you so wanted. That's a much more involved process and a very limited, but with those kinds of processes, you can actually see data real time. So just like if a patient was sitting in a CCU.

But you can imagine if I'm looking for something like AFib, which is intermittent when it first starts in almost everyone, it's paroxysmal, the ability to get an EKG on someone when they experience AFib is virtually impossible. So the ability to capture these rhythm disturbances with these implantable devices really has changed how we monitor patients.

And this is surveillance on a patient that I had a Fabry patient with a female interestingly enough, who kept having syncopal episodes and everyone thought that she was just orthostatic, hypoglycemia and are the usual kinds of iterations. And so we put a loop in her and she actually had ventricular tachycardia, as you can see here on the strip. She underwent an elective implantable cardioverter-defibrillator replacement and was successfully shocked twice after that. So showing that really what was driving her syncope was, one, she was having a life-threatening arrhythmia, but we would have never captured it if we hadn't gone with more of an invasive surveillance approach.

As I mentioned, we'll give you some high level stuff too that's not specific to lysosomal disorders. And part of what I was asked to speak to is atrial fibrillation. So as I told you, we know that it's commonplace for atrial fibrillation to be seen in Fabry, for example, like I say, probably at least one in five and probably more than that. And the question is, well, what do you do with it? And so we know that there are certain people that are at risk of having atrial fibrillation. And obviously in our populations, Fabry would be one of those. But in my world, a patient with heart failure with preserved ejection fraction would be at a high risk of having atrial fibrillation, for example.

So the question is, what do you do about it? And this is a reason that you could apply to any patient or yourself or your family members for how you are really diagnosing and managing atrial fibrillation. Very common, as we all know, it becomes incidence goes up as the patient ages, as the population ages. But what we would typically see is an echo as a new onset atrial fibrillation. Doing basic electrolyte evaluation, make sure it's not driving the AFib and obviously a thyroid function test just because we know hypothyroidism and hyperthyroidism can ultimately lead to atrial fibrillation, which would be great if that were the reversible cause.

The biggest things that we pay attention to are really around the stroke risk. So AFib in and of itself, it can cause problems, you can cause symptoms. If you have a rapid ventricular response it could become uncomfortable, you could even become syncopal, but it's not usually life-threatening. What's life-threatening are the strokes that are the subsequent downstream effects of having atrial fibrillation. So the biggest things we do on all of our patients is the idea of calculating a CHA2DS2-VASc score. And that's a score that we use based on presence of heart failure, your gender, other things that help us to understand what your overall risk of having a stroke. And if your score is at a certain level, as you see here, two or greater in men and three or greater in women, we would talk about oral anticoagulation therapy.

And this is just a continuation of that diagram. What do we like to do? Well, in cardiology, we do one of two pathways to manage the rhythm itself independent of the thromboembolic risk. One is a rhythm control strategy, and the other is a rate control strategy. Rhythm control is often what people will pursue that you see in the current era. And we use different kind of drugs, and you see some of those

listed on these slides. The problem is all anti-arrhythmics are potentially pro arrhythmics. So if I put someone on Sotalol or amiodarone, I need to be aware that I may be suppressing the AFib, but I may actually be promoting other ventricular disturbances, so we have to use them with caution. And they have their own unique side effects such as prolonging the QT interval.

But you see here, we decide based on their ejection fraction, which conduit or pathway we're going to go down. What we see more commonly nowadays is the idea of an ablative procedure. So is there someone who I could potentially cure them of their arrhythmia? And we won't talk about how to do that today, but usually those are for patients who have been on therapy and they fail or they are on therapy and they continue to be symptomatic, we would talk to them about an ablation and it's usually isolating the pulmonary veins is the typical approach.

Some people employ rate control, blockers, calcium channel blockers can be used. But we know in our Fabry populations, we're sometimes more cautious to use beta blockers because we already know as we started out with the initial ECG finding we see as sinus bradycardia, if I suppress that heart rate even more, I may make them more symptomatic. And obviously if they had conduction system disease, I would really want to be very careful about using something like a beta blocker or even a calcium channel blocker for rate control just because I may actually make the patient feel a lot worse. So that's the general overview of how we would approach atrial fibrillation in 2026 and broadly applicable to patients with lysosomal disorders, just remembering some of the nuances that we just talked about.

The other piece that was this idea of phenotypes, and we'll just briefly hit on this. Conventionally, there are typically about five phenotypes we talk about as a cardiomyopathy doctor, and we'll talk about that in just a minute, but this gives you an idea of what those sort of look like and what happens over time. So on the left, you see a normal myocardium, and then you see ventricular remodeling, which is what happens regardless if it's ischemia or deposition. We're seeing remodeling at the myocardial level, which is really about changing the shape of the ventricle. And you see that we're going from a relatively normal ventricle, to the top slide to a dilated ventricle. This would be a dilated cardiomyopathy.

The bottom slide goes from a normal heart to that intermediate fixture, which is a hypertrophied heart. So that should give you some ideas about how we think about remodeling and how we lead from normal physiology to a heart failure with reduced ejection fraction or with heart failure with preserved ejection fraction.

The different phenotypes that we see are dilated, hypertrophic, restrictive, non-compacting. Those are all phenotypes that can be seen in lysosomal disorders. And I want to go just a little bit faster in the interest of time.

Echo is what we use as our workhorse in imaging. And you can see here this, I didn't put moving images because I thought it was just easier to see, but on the left is a normal heart, and that thing in the center is the left ventricle. On the right, you see a hypertrophied ventricle. So this would be characteristic of someone with Fabry disease. Similarly, the short axis you see, the left is relatively normal myocardium cutting to heart like a donut, and on the right is extreme symmetric hypertrophy.

There are additional things we can do on imaging to detect myocardial involvement. And one of the most common things we use now is strain imaging, and I'm sure all of you have heard about this. And this can be done with any echo machine that you would probably have access to with the addition of some software. And what you see is we're actually characterizing the myocardium at all these little tiny points around. We draw little dots around the left ventricle. What we're seeing is how much areas, those discrete areas thicken and relax. So how much do they thick and how much do they shorten?

And we can actually represent that in a color coding where as you see on this slide on the left where it's all red depicts that all of the myocardium is contracting and relaxing in a synchronized way, in an

appropriate way. So that myocardial strain is normal. And it's read out as a negative number and more negative is typically better, counterintuitively in this situation.

We see on the right, you see a lot of different color patterns that are red, yellow, green, orange, and that tells us that we have myocardium that is not functioning appropriately. Even though this patient has a normal ejection fraction, which is what we would conventionally leverage in an echo lab, they have abnormal strain imaging. Not only the strain, but also the strain rate, so how quickly it's actually thickening and relaxing or shortening. And so you see this as a potential conduit to diagnose early cardiovascular phenotypes echocardiographically in the echo lab.

The thing we rely on as a cardiomyopathy provider progressively, though, is cardiac MR. The reasons are pretty simple. One is it's highly reproducible. It gives us all of this precise 3D imaging volumetric data. It gives me wall thickness data. It gives me all the chambers, it gives me the aorta, the vasculature, but the biggest thing is that I get is a thing called myocardial characterization. And we know that the earliest evidence of involvement in Fabry is this change in not only the T1 signaling, but ultimately we also see changes in scar burden.

And so if you've ever heard about an MRI, they usually give contrast and that contrast agent is called gadolinium. And in a normal heart, we inject the gadolinium and it goes through the heart muscle through the capillary bed and then it is cleared out and so that the image looks very homogeneous. In that particular scenario, the heart would look all black, for example.

In this example, you see we gave gadolinium and it got stuck in the tissue. So you see this black area of heart muscle that then has these arrows pointing to areas of white contrast tissue there. That's where you're seeing the gadolinium being stuck in the myocardium, and that's basic where it's not cleared, that's a surrogate marker of scar, and that's called late gadolinium enhancement. So that's what we would consider a scar burden or fibrosis burden on CMR.

That unfortunately requires gadolinium exposure, and gadolinium has limitations for people that have concomitant kidney disease. So we've come up with alternative strategies to be able to diagnose cardiovascular and myocardial involvement without exposing patients to gadolinium, and that is T1 mapping.

A native T1 mapping can essentially give me the same data without having to look at a contrast agent, which could be contraindicated if they have kidney disease or it could worsen kidney disease. And you see on this slide here, these techniques have been around a long, long time. You see the idea of T1 mapping where you have this nice homogeneous green circle, which represents the left ventricle. That's a normal patient.

And then when we do the T1 mapping here, you compare those patients. One, you can see that the circle or the donut is much thicker, which is indicative of left ventricular hypertrophy, but you also see this heterogeneity of the color patterns there, and that's telling us about abnormal T1 mapping. And when we actually gave that same patient gadolinium, you can see that this large sort of orange, red burden in the lateral wall here actually is very much maps out where we're seeing late gadolinium enhancement for a patient that actually did receive gadolinium contrast.

We also can do fancier techniques. And you heard about this at the beginning, the idea of the extracellular matrix or volume. So remembering that the cardiomyocytes live inside this network of the ECV, and you see this here depicted in the slide. We've essentially digested away all of the cardiomyocytes and what's left is that scaffolding or that ECV. And that's really important because that can contract or expand over time. And you can imagine if that expands, that can have implications directly on cardiomyocyte function, but it also in and of itself is an predictor of outcomes, which can be pretty bad.

It's definitely a driver of morbidity and mortality. This is just a slide depicting other causes. Whenever you see a cardiomyopathy in clinic, what are the non-ischemic causes? And obviously we see infiltrative disease as one of those potential.

I'm going to go through this relatively quickly in the next five minutes because you can read about this at your own leisure and you can find these references online at the ACC or the HA. But I think it's important for you to understand if you're dealing with heart disease and you're talking to a cardiologist, what are they actually talking about? So we have basically four buckets, and this was recently changed, where there usually was basically two: heart failure reduced ejection fraction, heart failure preserved ejection fraction. We define those purely by the ejection fraction itself. So if you say someone heart failure with reduced ejection fraction, that means their EF is 40% or less. If it's improved, that means it started at 40% or less, and now it's gone up to greater than 40%, and that's going to be in the face of medical therapy, treatment of their myocarditis, whatever the case may be.

We have a mid-range or mildly reduced ejection fraction, which captures 41 to 49, and then HFpEF, heart preserved ejection fractions and EF 50% or greater. That matters because the treatment paradigms are very much dictated by where your EF is, and we'll just go through those quickly. So for heart failure with mildly reduced ejection fraction, in the past, we actually would've only treated their blood pressure or other obesity, their sleep apnea, because we didn't have clear indications for what to use for people who have mildly reduced ejection fraction. Now, we actually would recommend SGLT2 inhibitors. So drugs in the US, it would be dapagliflozin or empagliflozin is what we would recommend, and then we would use diuretics as needed.

And this is important simply because if you're going to give these drugs, you'd have to be monitoring the kidney function of the patient at the same time. And then these are just how this has been reclassified over time. But what I want to spend time on is what you do with people that have this sort of hypertrophic phenotype. So that's really more for people when we're talking about they have depressed systolic function.

And remembering when we talk about Fabry or Pompe, these are HCM phenocopies. They're not the traditional true hypertrophic cardiomyopathy. True hypertrophic cardiomyopathy is typically defined as a sarcomeric mutation. So a tropomyosin mutation for a betamycin-heavy chain mutation would be the traditional HCM patients. We think about diseases like Fabry more as a HCM phenocopy because of the mechanism of disease, it's not a sarcomeric-based mutation. But this at least gives you [inaudible 00:44:58] how people are going to be thinking about how to manage patients with Fabry or other diseases that are lysosomal based with thickened myocardium.

So the first thing they're going to think about is if the patient obstructed or not. So you have a thick myocardium, you're doing echocardiography, you're trying to assess, does the patient have an obstructive physiology outside the left ventricular outflow tract? If they don't, we usually are managing other situations and we won't spend [inaudible 00:45:28] that today. But if they're obstructed, that's an opportunity for us to improve their symptoms. Most of those patients are going to be symptomatic if they have a significant obstruction and it's usually going to be with exertion. And we would use some sort of therapy to try and open up that outflow tract to relax that myocardium, essentially is what we're trying to do to make it less vigorous when it squeezes. And that's usually going to be accomplished by either a beta blocker or a calcium channel blocker. We just talked about some of the potential concerns we have to employ in a Fabry patient, for example, by using beta blockers or something like verapamil. So just wanted to be cognizant of that.

In the current era for true sarcomeric HCM, there's a new class of drugs called myosin inhibitors. It's a drug called mavacamten or Camzyos. You probably see it advertised on TV that actually works at the myosin level itself to reduce the sort of nature and strength of this cross-bridging that occurs at the

sarcomeric level. And that is a drug that is widely used now in HCM, but it has not been approved at this point for Fabry. And the other thing is the question is always about ICD, who needs a defibrillator? Complicated. We have some forays at a scoring system for Fabry, but they're probably not as robust as I would like for them to be. This is how we would traditionally think about a patient with sarcomeric-based HCM and should they get a defibrillator. If they've had sudden cardiac death, VF or sustained VT, we would think about it as a class-one indication.

If you have one of these, a family history of sudden death, massive LVH, that's going to be more than three centimeters on echo, unexplained syncope, an apical aneurysm, or if your ejection fraction is starting to decline, we would think strongly about an ICD. So this just at least gives you some of the ways we think about decision making in people with sarcomeric disease and ICD consideration.

This is back to how we would treat some of the heart failure with reduced ejection fraction patients. And once again, this is a lot of information to digest, but if we're really talking about cardiovascular care in patients with lysosomal disorders, this is part of the discussion is how do we manage their reduced ejection fraction, their systolic dysfunction? And these are the therapies that we would typically employ.

An RNA is an angiotensin receptor neprolysin inhibitor drug, and that's [inaudible 00:47:58]. And then we use things like beta blockers, MRAs like Apleuron or spironolactone, SGLT-2s, as we talked about. And these are the therapies we would ... This is called four-pillar therapy, and this is what we would use on everyone with an ejection fraction less than 40% unless there was a contract indication.

Unfortunately, many of our patients still progress to the right of the screen where they become more and more symptomatic, where they're getting admitted to the hospital, and we have a staging system where our end stage is stage D. And stage D ultimately requires consideration of maybe three options, and you could do an investigation. But one would be what's called durable mechanical circulatory support. I'm going to show you what that means in just a second. Second would be cardiac transplant, and third would be palliative care.

So this is how we approach most patients in the United States now with end stage heart failure. We have capped the number of transplants we can do traditionally over the last 30 years because we have a finite number of donors. Unfortunately, the number of people progressing to stage D heart failure only continues to increase. So we came up with a solution, and that solution is a left ventricular assist device. And what that truly means is that we put a pump in the apex of the left ventricle that sucks out the blood it goes through a returning sort of tube. So it's a centrifugal pump here. It pumps that blood up into the aorta, and then through the aorta the blood goes to the rest of the body. So we're essentially bypassing the need of the contractility of the left ventricle, and then there's a driveline that comes outside to the body that hooks up to a battery pack. We did more LVADs in the United States than we did in heart transplants last year because of the need. And the question is always, can we do an LVAD in a patient with a lysosomal disorder? And the answer is absolutely, yes. LVADs have been employed successfully in patients with Fabry disease and the outcomes have been quite good.

So you know there are two ways to think about LVAD therapy. One is a thing called destination therapy, which is this is your solution where you're going to get an LVAD and you're going to live with that for the rest of your life. The second is a bridge to transplant. And that's where we've seen LVADs used successfully in Fabry is the bridge from, "I have a failing heart but I need a transplant. How do I go from here to there?" It's through an LVAD, and that's what's called bridge to transplantation.

And so the question inevitably comes up is: can transplant be performed in lysosomal disorders? And the answer is yes. I've spent a lot of my life doing pediatric transplant medicine and obviously adult transplant medicine. And we know that cardiac transplant is a potential option, but it has to be in an appropriate patient. Successful outcomes have been documented both in Fabry and in Danon. Danon

has a larger experience, historically, mostly more case reports in Fabry, but compelling data. And interestingly, in Fabry, we've actually gone and done combined organ transplant or done heart and kidney, for example, concomitantly. And the important takeaway is here is that these reports unequivocally support the idea that lysosomal disorders are not a contraindication to heart transplant or organ transplant.

So I know we're almost at time. I'm going to skip over some of this AI stuff. One thing I do want to mention just in passing is I do a lot of work in the hypertrophic cardiomyopathy space. And we know this is a real opportunity to increase awareness and treatment opportunities in lysosomal disorders. It turns out two to 3% of patients that are called hypertrophic cardiomyopathy may be Fabry disease. And you think about that, the prevalence of HCM is conservatively probably one in 500 individuals, and it may be closer to one and 250. So if say two to 3% of those are Fabry patients, that's a huge opportunity on the research side, one, to identify more patients with lysosomal disorders, but more importantly, inject more funding into that pathway to identify potential therapeutic options.

So to conclude, broad spectrum of disease. What I've explained to you today pretty much is the entirety of cardiovascular medicine. We didn't talk a lot about PAD, but we really are touching a lot of bases. And so I hope what you take away and the providers take away is that you should really have an expansive thought process when it comes to caring for patients with lysosomal disorders and cardiovascular disease because you can see almost anything.

Increasing important cause of morbidity and mortality. Ultimately, in my world, and in yours, I'm sure it's always been about the delayed diagnosis. Anything we can do to get further upstream, earlier diagnosis, earlier intervention, earlier screening for me leads to earlier opportunities to bend the curve on the cardiovascular side.

This is my email. Please feel free to reach out if I can help. And with that, I will stop and turn it back over to Ozlem. And thank you all for your attention.

Ozlem Goker-Alpan:

Thank you, Dr. Jeffries, for this very detailed and informative presentation. We work closely with the cardiology group, but we have a problem with actually prior authorizing the ICD placement in patients with Fabry disease because I think they're not direct guidelines. And written for patients with Fabry disease, I think the pathophysiology is a little bit different than the hypertensive cardiomyopathy, which the ICDs actually are more prominently placed in. And other heritable disorders like amyloid cardiomyopathy. I think these are not representative of Fabry disease cardiomyopathy. Could you a little bit comment on the ICP placement and then the percentage of the fibrosis? Because this becomes actually more relevant in a female patient that does not have this massive cardiomyopathy that as we see in males, but they do have extensive, some of them actually do have extensive fibrosis without overt cardiomyopathy.

John Jefferies:

Great point. Well, first of all, the question are most cardiologists familiar with this information? I would say unfortunately not. So part of my job and everyone else's job is to increase awareness and advocacy in that direction. I think it's getting better, mostly because HCM has become a more prevalent player in adult cardiology because of this new drug that's offered, the mavocamten drug. So now people are thinking about it more. And if they observe class one recommendations, they're doing genetic testing and through that genetic testing, they're going to identify potential patients such as Fabry. So I do think it's getting better in sort of a backdoor kind of way, but it's definitely not where it needs to be.

Great point about ICD. So one of the other indications that people leverage for ICD placement and traditional HCM is scar burden. And most people would say if it's 15% or more of the left ventricular mass, that that is a threshold to consider a defibrillator. And to Ozlem's point, I have leveraged those same data to argue for ICD placement in Fabry patients. And so that is at least an anchor that the insurers have that they know about. And oftentimes, unfortunately, it requires a peer-to-peer discussion has been my experience. I can have my team call and there's like, "No. Blah, blah, blah." And once you go in and say, "Listen, I know that this patient is at high risk. Yeah, I'm realigning risk factors from traditional HCM to Fabry, but that's what I have."

And I think anyone with common sense would understand if you have nearly one-fifth of your myocardium with scar, we know that that's a nidus of ventricular arrhythmias. You don't need to be an electrophysiologist for that. So that's how we leverage it. But important information, because we have some people with mild thickness, but really profound scar burden, so those patients actually may be more of a risk than traditional patients at risk for sudden death, so it's an excellent point.

But as far as the insurance and stuff, that just requires a lot of elbow grease in our experience to get it done.

Ozlem Goker-Alpan:

Yes, exactly. And we have actually, there are ... So we see patients from several states, means for some states it is not as cumbersome, but I think in Virginia. It's really a big issue. And I need to reemphasize that whoever we recommended ICD and didn't get it, unfortunately they passed away. So that is really, really important and that these patients suffer actually sudden death without any explanation.

John Jefferies:

I'm sorry, just one building block on that that you may want to think about and that the listeners could also employ. There is a bridge that sometimes we use radiology between ventricular arrhythmias and syncope to an ICD, and it's a thing called a life vest. And so if you have difficulties getting defibrillators, sometimes we have employed that very rarely for patients. It's truly a wearable device that is an external shock, not quite as effective as an implanted device, but it's pretty good. Obviously the caveat is they have to be wearing it for it to actually make a difference, but that is something else. If you're struggling to get a defibrillator and it's going to be three months, four months, five months, and you think this patient's really at risk, that is a bridge opportunity.

Ozlem Goker-Alpan:

Actually, we are running out of time, but I do have one more important question, I think, with the AFib management. And since you mentioned the ablation is becoming more acceptable, the reason is about a decade ago, we were sending patients for consideration ablation and it was like, that is the oral anticoagulants. And the patients rarely actually can tolerate all oral anticoagulants. And I've seen patients having major strokes on Coumadin and similar oral anticoagulants. And then you have these repetitive strokes and the patients develop progressive dementia. So the dementia risk is much more higher with a patient, not only Fabry disease, but also having repetitive AFib. So how can we actually send a patient for consideration for ablation before we consider a certain period of oral anticoagulants, and so forth?

John Jefferies:

Yeah. So the anticoagulation is purely predicated on the CHA2DS2-VASc score. And I will send a link to the organizers about where you can go to and actually calculate a CHADS-2 VASCOR. And if you're a male or female at a certain threshold, then oral anticoagulation is recommended regardless of your burden of AFib. You could be permanent, you could be proxysmal. And Fabry or in lysosomal disorder is really important. We recommend these direct oral anticoagulants over Warfarin because I agree with you completely. It's just not sufficient. So that would be drugs like Eliquis or apixaban is the name of rivaroxaban, or Xarelto is the other drug. That's what we would typically recommend.

The real indication Addition for the ablation is more about if you're still having symptoms or you fail a traditional antiarrhythmic or rate control approach. We're getting closer and closer. We're offering that as a first-line therapy. But be cognizant the anticoagulation is in this column and then the actual rhythm management is this column. And that anticoagulation is purely based on your CHA2DS2-VASc. But I will make sure everyone has a link to that website. You literally just go ahead and plug the numbers in and it will tell you what your risk is.

Ozlem Goker-Alpan:

And one last thing is about Watchman. We have some patients who had Watchman implants.

John Jefferies:

Watchman's a great device. There's some data we just presented at the ACC two weeks ago. It may not be quite as good as the oral anticoagulants at preventing stroke. So for those on the call, apologize. A Watchman, basically the manmade device that we go in to isolate the left atrial appendage. So off of the left atrium is a little dog ear that comes off, and that's where most of the clot forms in AFib. What we do is mechanically wall that off. So if there's a clot inside this pouch, it can't get out to the systemic circulation. That is a Watchman device or what's called a left atrial appendage occluder device. They work well. And it does help people who can't tolerate anticoagulants, for example. It's an alternative pathway.

Ozlem Goker-Alpan:

Okay. Unfortunately, we have to finish with this presentation. Everybody's asking whether they could have a copy of the presentation. It's going to be on the CheckRare (www.checkrare.com) website. And then you can access Dr. Jeffries' email there too. And you have my email. I'll be happy to assist the audience if they have any further questions as well.

So I would like to actually present our deepest gratitude again for Dr. Jeffries, and hopefully we'll invite him again, and then we can actually continue with the discussion. And up until then, have a great year and have a great spring. And so see you soon in the next one.